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Are Uric Acid Levels Different from Healthy Subjects in Bipolar Affective Disorder and Schizophrenia?: Relationship Between Clinical Improvement and Episode Severity in Male Patients

Ürik Asit Düzeyleri İki Uçlu Bozukluk ve Şizofrenide Sağlıklı Bireylerden Farklı mıdır?: Erkek Cinsiyette Klinik İyileşme ve Dönem Şiddeti ile İlişkisi

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ABSTRACT

Introduction: Purinergic system dysfunction has been shown both in patients with bipolar disorder (BD) and those with schizophrenia. The aim of this study was to evaluate whether uric acid levels in male BD patients with manic episode and schizophrenia patients with psychotic relapse differ from healthy male subjects. Secondly to assess whether uric acid levels in both patient groups correlate with episode severity and if a decrease in uric acid levels correlate with clinical improvement.

Method: A total of 55 BD patients with manic episode and 59 schizophrenic patients with psychotic relapse were evaluated at baseline and at weeks 1, 2, 3 using the Young Mania Rating Scale (YMRS) and the Positive and Negative Syndrome Scale (PANSS), and their plasma uric acid levels were measured. 60 age-matched healthy males without history of any previous or current psychiatric diagnosis and treatment constituted the control group. In order to determine plasma uric acid levels, blood samples were centrifuged at 3000 x g for 15 minutes, stored at -80°C and measured in milligrams per deciliter.

Results: Uric acid levels in both patient groups with manic episode and psychotic relapse were found higher than in healthy controls (f=6.122, p=.027). The difference between repeated measurements of uric acid levels in BD patient group was found to be between baseline and first week measurements (after Bonferroni correction) (p<.001). No correlation was found between YMRS and PANSS scores and uric acid levels at 4 assessment times.

Conclusion: Uric acid levels in male BD and schizophrenia patients with manic episode and psychotic relapse were similar with each other, and higher than in healthy males. No correlation was found between uric acid levels and episode severity in both groups. However, for patients with BD, a decrease in uric acid levels between baseline and first week seems to be correlated with clinical improvement. *(Archives of Neuropsychiatry 2014; 51: 229-232)*

Key words: Bipolar disorder, schizophrenia, uric acid

Conflict of Interest: The authors reported no conflict of interest related to this article.

ÖZET

Giriş: Pürinerjik sistem işleyişindeki bozulma hem iki uçlu bozukluk (İUB), hem şizofreni tanılı olgularda gösterilmiştir. Bu çalışmanın amacı İUB ve şizofreni tanılı erkek olgularda manik dönem ve psikotik alevlenme sırasındaki ürik asit düzeylerinin, sağlıklı erkeklerden farklılaşıp farklılaşmadığının araştırılmasıdır. İkinci olarak her iki tanı grubunda ürik asit düzeylerinin dönem şiddeti ile, ürik asit düzeylerindeki azalmanın klinik iyileşme ile ilişki gösterip göstermediğinin incelenmesidir.

Yöntem: Bu amaçla 55 İUB, 59 şizofreni tanılı olgu manik dönem ve psikotik alevlenme döneminin başında, 1., 2. ve 3. haftada YMDÖ ve PANSS ile değerlendirilmiş, plazma ürik asit düzeyleri ölçülmüştür. Kontrol grubu diğer iki grupla yaş ortalaması benzer, önceki tanı ve tedavi öyküsü olmayan ve şimdiki psikiyatrik yakınması bulunmayan 60 sağlıklı erkektir. Plazma ürik asit düzeyleri 3000 devirli santrifüjde 15 dakika çevrilerek, -80°C, mg/ dl cinsinden kaydedilmiştir.

Bulgular: Hem İUB hem şizofreni tanılı erkek olgularda manik dönem ve psikotik alevlenme sırasındaki ürik asit düzeyleri sağlıklı erkeklerden yüksek bulundu (f= 6,122, p=,027). İUB tanılı erkeklerde yinelenen ölçümler arasındaki fark (Bonferroni düzeltmesi ile) başlangıç ile 1. hafta ürik asit düzeyleri arasında saptandı (p<,001). Her dört ölçüm için YMDÖ ve PANNS puanları ile ürik asit düzeyleri arasında bir korelasyon gösterilemedi.

Sonuç: İUB ve şizofreni tanılı erkek olgularda manik dönem ve psikotik alevlenme sırasındaki ürik asit düzeyleri birbiri ile benzer olup, sağlıklı erkeklerden yüksektir. Her iki grupta ürik asit düzeyleri ile dönem şiddeti arasında bir bağıntı bulunmamıştır. Ancak İUB tanılı olgularda ürik asit düzeylerinde başlangıç ve birinci hafta arasındaki azalma, klinik iyileşme ile ilişkili görünmektedir. *(Nöropsikiyatri Arşivi 2014; 51: 229-232)*

Anahtar kelimeler: İki uçlu bozukluk, şizofreni, ürik asit

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Introduction

Uric acid is the final product of purine metabolism and is produced by xanthine dehydrogenase. Increased levels of uric acid indicate accelerated purinergic transformation and decreased adenosinergic conduction (1). Adenosinergic receptors limit cellular excitability by inhibiting neurotransmitter release in the central nervous system (CNS).

The purinergic system is involved in the regulation of mood, motor activity, cognitive function, sleep, and behavior (2). Lesch–Nyhan syndrome, which is characterized with dysfunction in the purinergic system, can be exemplified as one of the states of disinhibition where uric acid is produced in large amounts. Increased uric acid levels in individuals who do not have any psychiatric diagnosis are associated with high impulsivity and hyperthymic and irritable temperament properties (3).

Increasing evidence indicates that dysfunction in the purinergic system is involved both in bipolar disorder (BD) and in the pathophysiology and treatment of schizophrenia (4,5). However, uric acid levels were found to be lower in both chronic schizophrenia patients and newly diagnosed schizophrenia patients than healthy individuals, despite increased uric acid levels shown in both chronic BD patients and first episode mania patients (6,7,8,9,10,11). In our clinical practice, increased uric acid levels found in patients with a diagnosis of schizophrenia who presented with psychotic exacerbation are not compatible with these findings.

The aim of this study was to investigate whether uric acid levels at the time of the manic period and psychotic exacerbation in male patients with a diagnosis of BD and schizophrenia were different from healthy individuals. The secondary aim was to investigate whether uric acid levels were related with episode severity and clinical improvement in both diagnosis groups.

Methods

Sample

With this objective, 55 subjects with psychotic findings diagnosed with BD and manic episode according to the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) and 59 subjects with a diagnosis of schizophrenia who were admitted to our ward from the emergency department and whose relatives gave informed consent were consecutively included in the study. The subjects who had gout, chronic inflammatory disease, or any other disease related with hyperuricemia were excluded. The control group was composed of 60 age-matched healthy men who had no previous history of any diagnosis and treatment and who had no current psychiatric complaints. The weekly scale and laboratory data used in routine patient follow-up were used in the study.

Scales

Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I)

The Turkish validity and reliability study for the form prepared by First et al. (12) to investigate Axis 1 psychiatric disorders by DSM-IV was performed by Özkürkçügil et al. (13).

Young Mania Rating Scale (YMRS)

This scale was used to show the severity of manic symptoms before treatment and the state of well-being in the period of well-being. This scale, which is filled in by the interviewer, was developed by Young et al. (14), and its Turkish validity and reliability study was performed by Karadağ et al. (15).

Positive and Negative Syndrome Scale (PANSS)

This is a 7-score semi-structured interview scale developed by Kay et al. including 30 items (16). Of the 30 psychiatric parameters, 7 belong to the positive symptoms subscale, 7 belong to the negative symptoms subscale, and the remaining 16 belong to the general psychopathology subscale. The Turkish validity and reliability study of the scale was performed by Kostakoğlu et al. (17). The internal consistency for the Turkish version of PANSS ranged between .71 and .75, the intra-group correlation coefficient was calculated to be .96, and the correlation coefficient of the positive and negative subscales was calculated to be –.41.

Application

The diagnoses were made by the psychiatrists who worked in the male psychiatry ward using SCID-I according to DMS-IV. The patients with BD were evaluated using YMRS and the patients with schizophrenia were evaluated using PANSS at the time of admission to the ward (in the beginning of the manic phase and psychotic exacerbation) and in the 1st, 2nd, and 3rd weeks of treatment, and plasma uric acid levels were measured. Plasma uric acid levels (in mg/dL) were recorded after centrifuging at 3000 rpm for 15 min at –80°C.

Table 1. Age, disease time, and uric acid levels in the beginning of treatment in patients with a diagnosis of bipolar disorder and schizophrenia and in healthy individuals

	BD (n=55)	Schizophrenia (n=59)	Control (n=60)	Analysis	
				f/t	p
Age (mean±SD)	37.9±11.9	40.3±11.5	34.2±10.3	.880	.650*
Disease time (Years) (mean±SD)	12.5±6.3	14.1±8.7	-	.248	.805**
Uric acid levels (mean±SD)	6.06±1.48	5.55±1.89	4.4±.9	6.122	.027*

*One-way ANOVA, **Student's t-test

Statistical Analysis

The study data were evaluated using a computer software called the Statistical Package for the Social Sciences (SPSS; ver. 15.0) Student's t-test and one-way analysis of variance (ANOVA) were used to compare numerical data. To compare repetitive measurements in the same subjects, repeated measures ANOVA was used, and the Bonferroni correction t-test was used if a difference was found. Pearson's correlation analysis was used in correlation analysis. All tests were two ended, and a p value of <.05 was considered significant for all tests. In the tests where Bonferroni correction was applied (shown in Tables 2 and 3), a p value of <.012 was considered statistically significant.

Results

Uric acid levels were found to be higher in both BD and schizophrenia patients at the time of the manic period and psychotic exacerbation than those in healthy men (f=6.122, p=.027), (Table 1). No statistically significant difference was found in terms of initial uric acid levels between the patients with a diagnosis of BD and schizophrenia (p=.108).

The difference between the uric acid levels measured at the baseline and in the subsequent weeks was evaluated using repeated measures ANOVA. A statistically significant reduction was found between the measurements in the subjects with a diagnosis of BD (p=.015) (Table 2). As a result of the Bonferroni correction t-test performed subsequently, it was observed that the difference arose from the difference between the uric acid levels measured at the baseline and after the first week (p<.001). Although further reduction was observed in the uric acid levels after the first week, this difference was not statistically significant (p=.542). The reduction in the YMRS scores lost significance in the measurement after the 3rd week (p=.578). No statistically significant difference was found between the uric acid levels measured at the baseline and in the subsequent weeks in the patients with a diagnosis of schizophrenia. The reduction in the PANSS scores was found to be significant in the measurement after the 1st week (p<.001) (Table 3).

No correlation was found between the YMRS and PANSS scores for each of the four measurements. No correlation could be demonstrated between the reduction in weekly YMRS scores and the reduction in the uric acid level observed in BD with treatment (p<.05).

Discussion

In our study, uric acid levels in the subjects with a diagnosis of BD were found to be higher than individuals, which correlated with the literature (6,7). A significant difference was found between the uric acid levels measured in the beginning of the manic phase treatment and after the end of the first week in the subjects with a diagnosis of BD. A similar difference was observed between the YMRS scores obtained at the beginning, in the first week, and in the second week. In patients in the manic phase, a correlation was found between the reduction in the uric acid levels measured at the baseline and after the end of the first week and the reduction in YMRS scores. This underlines the possibility that uric acid is a manic phase-specific situational marker and its clinical significance. A similar correlation was shown in the study of Marchado-Vİeira et al. (6). On the other hand, no correlation could be shown between uric acid levels and YMRS scores in the subjects with a diagnosis of BD. This finding may be because the increased uric acid levels in the manic phase in patients with BD were not related with the episode severity. Thus, uric acid levels were not found to be correlated with episode severity in the study of Giacomo-Salvadore et al. (7), in which first attack mania patients were examined to eliminate the confounding factors, including the use of psychotropic drugs and chronicity.

Increased levels of uric acid means accelerated purinergic transformation and decreased adenosinergic conduction (1). Adenosinergic receptors limit cellular excitability by inhibiting the release of neurotransmitters in the CNS. Uric acid particularly regulates A1 receptors and is responsible of the antikindling action. This is thought to be the

Table 2. Weekly uric acid levels and YMRS scores during the course of treatment in patients with a diagnosis of bipolar disorder

	Baseline (mean±SD)	1st week (mean±SD)	2nd week (mean±SD)	3rd week (mean±SD)	Analysis	
					f	p
Uric acid	6.06±1.48	5.41±1.44	5.28±1.33	5.17±1.15	4.429	.015*
YMRS	26.25±8.71	18.23±7.92	10.52±6.00	8.34±3.17	30.05	.017*

*Repeated measures ANOVA

Table 3. Weekly uric acid levels and PANSS scores during the course of treatment in patients with a diagnosis of schizophrenia

	Baseline (mean±SD)	1st week (mean±SD)	2nd week (mean±SD)	3rd week (mean±SD)	Analysis	
					f	p
Uric acid	5.55±1.89	4.93±1.23	5.03±1.03	4.88±1.07	2.093	.152*
YMRS	109.84±30.5	88.84±29.2	75.03±26.3	66.42±16.1	23.56	.026*

*Repeated measures ANOVA

main relation between adenosinergic conduction and manic symptoms (18). Thus, lithium acts to decrease uric acid levels (19). On the other hand, a similar action has been observed with carbamazepine, whereas sodium valproate has been shown to increase uric acid levels (20). In a randomized controlled study, Machado-Vieira et al. (6) showed that the use of allopurinol, which is a xanthine dehydrogenase inhibitor, in combination with lithium was considerably efficient in the treatment of acute mania.

The literature related with dysfunction of the purinergic system in schizophrenia has reported that uric acid levels are lower in patients with chronic disease and with first manic episode than those in healthy individuals (8,9,10,11). In the patients with a diagnosis of schizophrenia who presented with a psychotic episode, uric acid levels were found to be similar to the patients with a diagnosis of BD who were in the manic phase and higher than those in healthy individuals in our study. In contrast to other studies, uric acid levels were examined in a population which consisted only of the male gender in our study. Uric acid levels are found to be higher in men than those in women (12). In addition, our patients with a diagnosis of schizophrenia were in the acute psychotic episode of the disease and had severe positive psychotic findings with baseline PANSS scores above 100. In our study, uric acid levels, which we found to be higher in contrast to the literature, may be specific for a portion of the subjects with a diagnosis of schizophrenia by definition.

In our study, uric acid levels were not found to be different at the baseline and in the subsequent weeks of treatment in the patients with a diagnosis of schizophrenia. Although a reduction in uric acid levels was observed between the baseline and the first week, the difference was not significant. On the other hand, a significant reduction was found in PANSS scores between the baseline and the first week. Thus, these findings suggest that uric acid levels are not correlated with clinical improvement in patients with schizophrenia presenting with a psychotic episode. In addition, no correlation could be shown between the PANSS scores and uric acid levels in these patients. In accordance with this finding of ours, Yao et al. (22) reported that uric acid levels returned to normal in first episode schizophrenia patients following the use of any antipsychotic drug for 4 weeks, but this did not occur in patients with chronic disease (11). In another study, it was shown that decreased uric acid levels were independent from the use of medication in schizophrenia patients in patients who were using haloperidol (9). This was explained by the fact that haloperidol had no effect on antioxidant enzymes (8). However, the hypouricemic effect of zuclopenthixol was shown by Bloch et al. in 1992 (23).

According to the findings obtained in our study and supported by the literature, increased uric acid levels in the manic phase in male patients with a diagnosis of BD appear to be independent from the episode severity but related with clinical improvement. In male schizophrenia patients with a chronic disease, uric acid levels, which were shown to be increased during a psychotic episode, appear to be a finding which is independent from the episode severity and improvement not reaching clinical significance.

References

1. Burnstock G. Purinergic signalling and disorders of the central nervous system. Nat Rev Drug Discov 2008; 7:575-590.
2. Jinnah HA. Lesch–Nyhan disease: from mechanism to model and back again. Dis Model Mech 2009; 2:116-121.
3. Lorenzi TM, Borba DL, Dutra G, Lara DR. Association of serum uric acid levels with emotional and affective temperaments. J Affect Disord 2009; 121:161-164.
4. Zarate CA Jr, Manji HK. Bipolar disorder: candidate drug targets. Mt Sinai J Med 2008; 75:226–247.
5. McQuillin A, Bass NJ, Choudry K, Puri V, Kosmin M, Lawrence J, Curtis D, Gurling HM. Case-control studies show that a non-conservative aminoacid change from a glutamine to arginine in the P2RX7 purinergic receptor protein is associated with both bipolar- and unipolar-affective disorders. Mol Psychiatry 2009; 14:614–620.
6. Machado-Vieira R, Soares JC, Lara DR, Luckenbaugh DA, Busnello JV, Marca G, Cunha A, Souza DO, Zarate CAJr, Kapczinski F. A double-blind, randomized, placebo-controlled 4-week study on the efficacy and safety of the purinergic agents allopurinol and dipyridamole adjunctive to lithium in acute bipolar mania. J Clin Psychiatry 2008; 69:1237–1245.
7. Salvadore G, Viale CI, Luckenbaugh DA, Zanatto VC, Portela LV, Souza DO, Zarate CA Jr, Machado-Vieira R. Increased uric acid levels in drug-naïve subjects with bipolar disorder during a first manic episode. Prog Neuropsychopharmacol Biol Psychiatry 2010 ;34:819-821.
8. Yao JK, Reddy R, van Kammen DP. Reduced level of plasma antioxidant uric acid in schizophrenia. Psychiatry Res 1998; 80:29-39.
9. Yao JK, Reddy R, van Kammen DP. Abnormal age-related changes of plasma antioxidant proteins in schizophrenia. Psychiatry Res 2000; 97:137-151.
10. Reddy RD, Keshavan MS, Yao JK. Reduced plasma antioxidants in first episode patients with schizophrenia. Schizophr Res 2003; 62:205–212.
11. Yao JK, Dougherty GG Jr, Reddy RD, Keshavan MS, Montrose DM, Matson WR, Rozen S, Krishnan RR, McEvoy J, Kaddurah-Daouk R. Altered interactions of tryptophan metabolites in first-episode neuroleptic-naive patients with schizophrenia. Mol Psychiatry 2010; 15:938–953.
12. First MB, Spitzer RL, Gibbon M, Williams JBW. Structured clinical interview for DSM-IV clinical version (SCID-I/CV). Washington: American Psychiatric Press; 1997.
13. Özkürkçügil A, Aydemir Ö, Yıldız M. DSM-IV Eksen I Bozuklukları İçin Yapılandırılmış Klinik Görüşmenin Türkçe'ye Uyarlanması ve Güvenilirlik Çalışması. İlaç ve Tedavi Dergisi 1999; 12:233-236.
14. Young RC, Biggs JT, Ziegler VE, Meyer DA. A rating scala for mania: reliability, validity, and sensitivity. Br J Psychiatry 1978; 133:429-435.
15. Karadag F, Oral ET, Yalçın FA, Erten E. Young Mani Derecelendirme Ölçeginin Türkiye' de geçerlik ve güvenirligi. Turk Psikiyatri Dergisi 2001; 13:107-114.
16. Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr Bull 1987; 13:261-275.
17. Kostakoğlu AE, Batur S, Tiryaki A. Pozitif ve negatif sendrom ölçeğinin (PANSS) Türkçe uyarlamasının geçerlilik ve güvenilirliği. Türk Psikoloji Dergisi 1999; 14:23-32.
18. Machado-Vieira R, Lara DR, Souza DO, Kapczinski F. Purinergic dysfunction in mania: an integrative model. Med Hypotheses 2002; 58:297–304.
19. Anumonye A, Reading HW, Knight F, Ashcroft GW. Uric-acid metabolism in manicdepressive illness and during lithium therapy. Lancet 1968; 1:1290–1293.
20. Ring HA, Heller AJ, Marshall WJ, Johnson AL, Reynolds EH. Plasma uric acid levels in patients receiving anticonvulsant monotherapy. Epilepsy Res 1991; 8:241–244.
21. Brooks SC, LinnJJ, Disney N. Serotonin, folic acid, and uric acid metabolism in the diagnosis of neuropsychiatric disorders. Biol Psychiatry 1978; 13:671-684.
22. Yao JK, Dougherty GG Jr, Reddy RD, Keshavan MS, Montrose DM, Matson WR, McEvoy J, Kaddurah-Daouk R. Homeostatic imbalance of purine catabolism in firstepisode neuroleptic-naive patients with schizophrenia. PLoS One 2010; 5:e9508.
23. Bloch M, Gur E, Shalev AY. Hypouricemic effect of zuclopenthixol: a potential Marker of drug compliance? Psychopharmacology (Berl) 1992; 109:377-378.